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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ROONEY, NORA MAUREEN	
ART UNIT	**PAPER NUMBER**
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/651,136	SIPKA ET AL.	
	Examiner	Art Unit	
	Nora M. Rooney	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *6-9,11,12,14-16,20 and 21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 10, 13, 17-19 and 22-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-24 are pending.

2. Claims 6-9, 11-12, 14-16 and 20-21 stand withdrawn from further consideration pursuant to 37 C.F.R. 1.142(b) as being drawn to a nonelected species.

3. Claims 1-5, 10, 13, 17-19 and newly added claims 22-24 are currently under examination as they read on a process for inhibiting allergic disease in humans by aerosol administration.

4. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 03/21/2007 has been entered.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-5, 10, 13, 17-19 and 22-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not reasonably provide enablement for: **a process for inhibiting development of allergic disease**, the process comprising exposing a neonatal or immature **mammal** or **bird** to irradiation detoxified lipopolysaccharide derived from bacterial endotoxin of claim 1; wherein the irradiation -detoxified lipopolysaccharide is detoxified by exposure of the endotoxin to irradiation at a level of from about 25 to about 150 KGy of claim 2; wherein the irradiation changes the structure of the endotoxin while maintaining its positive immune effect in the resulting irradiation-detoxified lipopolysaccharide of claim 3; wherein the irradiation-detoxified lipopolysaccharide is adapted to stimulate the Th 1 arm of the immune system of claim 4; wherein **an infant mammal** is exposed of claim 5; wherein the exposure is achieved by administering an aerosol spray composition comprising the irradiation-detoxified lipopolysaccharide of claim 10; wherein a human of 1 month to 2 years of age is exposed of claim 13; wherein exposure to the irradiation-detoxified lipopolysaccharide is achieved shortly after birth and during the maturing life cycle of the **mammal** or **bird** of claim 17; wherein exposure to the irradiation-detoxified lipopolysaccharide is achieved on a daily basis during growth of the **mammal** or **bird** of claim 18; wherein exposure to the irradiation-detoxified lipopolysaccharide is achieved on a weekly basis during growth of the **mammal** or **bird** of claim 19; a **process for inhibiting development of allergic disease**, the process comprising exposing

a neonatal or immature **mammal** or **bird** to irradiation-detoxified lipopolysaccharide derived from E. coli bacteria endotoxin of claim 23; wherein a human of 1 month to 2 years of age is exposed of claim 24.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

The specification on pages 7 to 10 discloses the preparation and use of irradiated LPS in a pressurized aerosol formulation, a manual pump aerosol formulation, a dry powder formulation, a cloth such as a diaper provided with irradiated LPS and a topical cream or lotion formulation with irradiated LPS. Table 1 discloses the results of IL-1 release in response to in vitro stimulation of peripheral blood mononuclear cells with irradiated LPS vs. native LPS.

Since no *in vivo* studies were used as model system to treat allergic disease, it is not clear that reliance on the *in vitro* data of Il-1 release by LPS-stimulated cells accurately reflects the animal efficacy of the claimed therapeutic strategy. The specification does not adequately teach how to effectively treat any allergic disease or reach any therapeutic endpoint in animals by administrating the therapeutic composition of irradiated LPS. The specification also does not

teach how to extrapolate data obtained from the *in vitro* studies to the development of effective in vivo animal therapeutic treatment, commensurate in scope with the claimed invention. Therefore, it is not clear that the skilled artisan could predict the efficacy of the irradiated LPS to inhibit allergic disease as encompassed by the claimed invention. There must be a rigorous correlation of biological activity between the IL-1 release form PBL and an *in vivo* effectiveness to establish a method of inhibiting allergic disease. The specification does not provide sufficient teaching as to how it can be assessed that treatment of allergic disease is achieved after the administration of the irradiated LPS of the invention.

Substantiating evidence may be in the form of animal tests, which constitute recognized screening procedures with clear relevance to efficacy in humans. See Ex parte Krepelka, 231 USPQ 746 (Board of Patent Appeals and Interferences 1986) and cases cited therein. Ex parte Maas, 9 USPQ2d 1746.

Although, the specification describes *in vitro* experiments, there is no correlation on this record between the in vitro studies and the various methods of inhibiting allergic disease in currently available form for humans, mammals or birds. It is not enough to rely on in vitro studies where, as here, a person having ordinary skill in the art has no basis for perceiving those studies as constituting recognized screening procedures with clear relevance to efficacy in humans or animals (emphasis added). Ex parte Maas, 9 USPQ2d 1746.

In addition, the specification fails to provide guidance as to how to totally inhibit (100%

inhibition) allergic disease. It is noted that allergic diseases range from food, drug, inhalant, and metal allergies to exercise-induced anaphylaxis, all of which have different disease courses and etiologies. There is insufficient guidance in the specification to support using irradiated LPS to completely inhibit all allergic disease.

Further, the application does not provide adequate support of inhibiting allergic disease in all mammals or birds. The specification does not provide support for the prevention of any single allergic disease in any single animal, mammal or bird. As shown in the art, birds do not have IgE or allergies (See in particular, PTO-892, Reference U, page 5, 'Ask the Expert' section; PTO-892, Reference V, page 612, right column, first full paragraph; and PTO-892, Reference W, page 153, first full paragraph). Therefore, there is no process is that is able to inhibit allergies that do not form. The art shows that inhibition of allergic disease in mammals is unpredictable. Bischoff et al. teaches that although much research has been done on mouse mast cells, human mast cells are functionally different from murine mast cells. Human mast cells play a key role in allergic inflammation, so human mast cell laboratory tools are needed (PTO-892, Reference X, in particular whole document, abstract, paragraph spanning pages 93 and 94, page 102, 'Future Directions' section). Kurucz et al. teaches that asthma is a complex syndrome linked to genetic elements and environmental factors. The mouse, rat, guinea pig, rabbit, sheep, monkey, ferrett, cat, dog, pig and horse models of asthma are discussed, especially with reference to differences in pathogenesis with human asthma, which is a unique disease in the animal kingdom. All models discussed in the reference are different from each other and react differently from human asthma. Therefore, inhibiting asthma in one animal model vs another

animal model is not straightforward and depends on many factors (PTO-892, Page 2, Reference U, In particular, whole document). The art of allergic inhibition is highly unpredictable and it would require undue experimentation by one of ordinary skill in the art to inhibit asthma in a single mammal, much less the claimed method of inhibiting all types of allergic diseases in all mammals and birds.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-5, 10, 13, 17-19 and 22-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Malling et al. (PTO-892, Page 2, Reference V) in view of Previte et al. (PTO-892, Page 2, Reference W).

Malling et al. teaches a process for inhibiting development of allergic disease, the process comprising exposing a neonatal or immature mammal (human) to lipopolysaccharide derived from bacterial endotoxin; wherein the lipopolysaccharide is adapted to stimulate the Th 1 arm of the immune system (In particular, page 217, last paragraph); wherein an infant mammal (human) is exposed (In particular, page 217, last paragraph, whole document); wherein the exposure is achieved by administering an aerosol spray composition comprising the lipopolysaccharide (In particular, page 216, right column, first paragraph); wherein a human of 1 month to 2 years of age is exposed (In particular, page 217, last paragraph, page 216, left column, last paragraph); wherein exposure to the lipopolysaccharide is achieved shortly after birth and during the maturing life cycle of the mammal (human) (In particular, page 217, last paragraph, page 216, left column, last paragraph and right column last paragraph to top of right column on page 217); wherein exposure to the irradiation-detoxified lipopolysaccharide is achieved on a daily basis during growth of the mammal (human) (in particular, page 216, left column up to end of first full paragraph); and wherein the exposure to the irradiation-detoxified lipopolysaccharide is achieved on a weekly basis during growth of the mammal (human) (In particular, page 216, left column up to end of first full paragraph).

The claimed invention differs from the prior art by the recitation of irradiation-detoxified lipopolysaccharide or irradiation-detoxified LPS derived from E.coli; wherein the irradiation - detoxified lipopolysaccharide is detoxified by exposure of the endotoxin to irradiation at a level of from about 25 to about 150 KGy; and wherein the irradiation changes the structure of the

endotoxin while maintaining its positive immune effect in the resulting irradiation-detoxified lipopolysaccharide.

Previte et al. (PTO-892, Page 2, Reference W) teaches the detoxification of the lipopolysaccharide of Salmonella typhimurium, S. enteritidis and E. coli and heat-killed Salmonella typhimurium using 4, 4.8 and 4.5 Mrad (about 25 to about 150 kGy) ionizing radiation to eliminate lethality, while retainining antigenticity and pyrogenicity (retained positive immune effect) (In particular, abstract, whole document).

One of ordinary skill in the art would have been motivated to use the irradiation detoxified bacteria of Previte et al. in the bacterial immunotherapy method of inhibiting allergic disease of Malling et al. because the bacterial immunotherapy method should be safe for use in infants and children and have no risk of toxicity. Previte et al. teaches that isolated LPS and LPS in bacteria can be irradiation-detoxified of its lethal determinants while still retaining antigenicity and pyrogenicity.

All the claims are included in this rejection because the bacterial vaccines containing gram-negative bacteria of Malling et al. inherently comprise LPS.

From the reference teachings, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the

invention was made, as evidenced by the reference, especially in the absence of evidence to the contrary.

9. Claims 1-5, 10, 13, 17-19 and 22-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Malling et al. (PTO-892, Page 2, Reference V) in view of Tarpley et al. (PTO-892, Page 2, Reference X) as evidenced by Shultz et al. (PTO-892, Page 3, Reference U).

Malling et al. has been discussed *supra*.

The claimed invention differs from the prior art by the recitation of irradiation-detoxified lipopolysaccharide or irradiation-detoxified LPS derived from E.coli; wherein the irradiation - detoxified lipopolysaccharide is detoxified by exposure of the endotoxin to irradiation at a level of from about 25 to about 150 KGy; and wherein the irradiation changes the structure of the endotoxin while maintaining its positive immune effect in the resulting irradiation-detoxified lipopolysaccharide.

Tarpley et al. teaches the radiation sterilization of many types of bacteria, including gram-negative bacteria E. coli, using .5 to 5.6 Megarep/hr (In particular, Table 1). Shultz et al. is being used as an evidentiary reference to show that 1 Mrad is 6.2×10^{19} e.v./g and that 1 Megarep is 5.24×10^{19} e.v./g. Therefore,1 Megarep is .84516 Mrad and 1 Mrad equals 10kGy.

Therefore, Shultz et al. used 47.3 to 4.2 kGy (about 25 to about 150 kGy) ionizing radiation to sterilize the bacteria. (In particular, abstract, whole document, Table 1).

One of ordinary skill in the art would have been motivated to use the irradiation sterilized bacteria of Tarpley et al. in the bacterial immunotherapy method of inhibiting allergic disease of Malling et al. because the bacterial immunotherapy method should be safe for use in infants and children and have no risk of infection or risk. Tarpley et al. teaches that bacteria can be irradiation-sterilized. Malling et al. teaches that antibiotics can be administered to clear infections caused by bacterial immunotherapy. It would be advantageous to use a bacterial vaccine with retained immunogenic properties without causing infection and disease, especially when administered to infants and children.

All the claims are included in this rejection because the bacterial vaccines containing gram-negative bacteria of Malling et al. inherently comprise LPS.

From the reference teachings, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference, especially in the absence of evidence to the contrary.

10. Claims 1-5, 10, 13, 17-19 and 22-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Malling et al. in view of Previte et al. (PTO-892, Page 2, Reference W) and Matricardi et al. (IDS submitted 10/04/2004; Reference AN).

Malling et al. has been discussed *supra*.

The claimed invention differs from the prior art by the recitation of irradiation-detoxified lipopolysaccharide or irradiation-detoxified LPS derived from E.coli; wherein the irradiation - detoxified lipopolysaccharide is detoxified by exposure of the endotoxin to irradiation at a level of from about 25 to about 150 KGy; and wherein the irradiation changes the structure of the endotoxin while maintaining its positive immune effect in the resulting irradiation-detoxified lipopolysaccharide.

Previte et al. has been discussed *supra*.

Matricardi et al. teaches prevention of allergy wherein an infant mammal (human) is exposed to gram-negative microbial products (page 465, 'Safety' section); wherein a human of 1 month to 2 years of age is exposed to gram-negative microbial products (In particular, page 464, 'Clinical Studies; section and page 465 'Safety' section; 'Probiotics' section); wherein exposure to gram-negative microbial products is achieved shortly after birth and during the maturing life cycle of the mammal (human) (In particular, page 464, 'Clinical Studies; section and page 465 'Safety' section); wherein exposure to gram-negative microbial products is achieved on a daily

basis during the growth of the mammal (human); and wherein exposure to gram-negative microbial products is achieved on a weekly basis during the growth of the mammal (human) (In particular, 'Conclusions and Perspectives' section page 464). Matricardi et al. also teaches that the administration of LPS is beneficial to treat allergy and that a less toxic LPS derivative with immunostimulating properties is preferred for treatment purposes due the severe endotoxic effects of LPS (In particular, page 468, section entitled 'Proposed rationale for use against allergies'). The reference also teaches that one should be cautious in administering living organisms to infants to prevent allergy because they have lower colonization resistance and are immunologically naive compared with adults. (In particular, 'Safety' section). Gram-negative microbial products inherently comprise lipopolysaccharide.

One of ordinary skill in the art would have been motivated to use the irradiation detoxified bacteria of Previte et al. in the bacterial immunotherapy method of inhibiting allergic disease of Malling et al. because Matricardi et al. teaches that administration of living organisms as probiotics must be regarded as potentially dangerous for infants who have lower colonization resistance and are immunologically naive as compared to adults (In particular, page 465 'Safety' paragraph). Therefore, the bacterial immunotherapy method of Malling et al. should be safe for use in infants and children and have no risk of toxicity. Previte et al. teaches that isolated LPS and LPS in bacteria can be irradiation-detoxified of its lethal determinants while still retaining antigenicity and pyrogenicity.

All the claims are included in this rejection because the bacterial vaccines containing gram-negative bacteria of Malling et al. inherently comprise LPS.

From the reference teachings, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference, especially in the absence of evidence to the contrary.

11. Claims 1-5, 10, 13, 17-19 and 22-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Malling et al. in view of Matricardi et al. (IDS submitted 10/04/2004; Reference AN) and Tarpley et al. (PTO-892, Page 2, Reference X) as evidenced by Shultz et al. (PTO-892, Page 3, Reference U).

Malling et al. has been discussed *supra*.

The claimed invention differs from the prior art by the recitation of irradiation-detoxified lipopolysaccharide or irradiation-detoxified LPS derived from E.coli; wherein the irradiation - detoxified lipopolysaccharide is detoxified by exposure of the endotoxin to irradiation at a level of from about 25 to about 150 KGy; and wherein the irradiation changes the structure of the endotoxin while maintaining its positive immune effect in the resulting irradiation-detoxified lipopolysaccharide.

Tarpley et al. and Shultz et al. have been discussed *supra*.

Matricardi et al. has been discussed *supra*.

One of ordinary skill in the art would have been motivated to use the irradiation sterilized bacteria of Tarpley et al. in the bacterial immunotherapy method of inhibiting allergic disease of Malling et al. because Matricardi et al. teaches that administration of living organisms as probiotics must be regarded as potentially dangerous for infants who have lower colonization resistance and are immunologically naive as compared to adults (In particular, page 465 'Safety' paragraph). Tarpley et al. teaches that bacteria can be irradiation-sterilized. Malling et al. teaches that antibiotics can be administered to clear infections caused by bacterial immunotherapy. It would be advantageous to use a bacterial vaccine with retained immunogenic properties without causing infection and disease, especially when administered to infants and children.

All the claims are included in this rejection because the bacterial vaccines containing gram-negative bacteria of Malling et al. inherently comprise LPS.

From the reference teachings, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the

invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference, especially in the absence of evidence to the contrary.

12. Claims 1-5, 10, 13, 17-19 and 22-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gereda et al. (PTO-892, Page 3, Reference V) in view of Matricardi et al. (IDS filed on 10/04/2004, Reference AN) and Tarpley et al. (PTO-892, Page 2, Reference X) as evidenced by Shultz et al. (PTO-892, Page 3, Reference U).

Gereda et al. teaches a process for inhibiting development of allergic disease, the process comprising exposing a neonatal or immature mammal (human) to lipopolysaccharide derived from bacterial endotoxin; wherein the lipopolysaccharide is adapted to stimulate the Th 1 arm of the immune system (In particular, page 1680, 'Introduction' and pages 1682-3 'Discussion' sections); wherein an infant mammal (human) is exposed (In particular, abstract, whole document); wherein the exposure is achieved by administering an aerosol spray composition (air) comprising the lipopolysaccharide (In particular, whole dodument); wherein a human of 1 month to 2 years of age is exposed (In particular, abstract, page 168, 'Participants' section); wherein exposure to the lipopolysaccharide is achieved shortly after birth and during the maturing life cycle of the mammal (breathing in home) (In particular, abstract, page 1680, 'Participants' section); and wherein exposure is achieved on a daily basis (breathing) during growth of the mammal (In particular, whole document); wherein exposure is achieved on a weekly basis (breathing) during growth of the mammal (human) (In particular, whole document).

The claimed invention differs from the prior art by the recitation of irradiation-detoxified lipopolysaccharide or irradiation-detoxified LPS derived from E.coli; wherein the irradiation - detoxified lipopolysaccharide is detoxified by exposure of the endotoxin to irradiation at a level of from about 25 to about 150 KGy; and wherein the irradiation changes the structure of the endotoxin while maintaining its positive immune effect in the resulting irradiation-detoxified lipopolysaccharide.

Tarpley et al. and Shultz et al. have been discussed *supra.*

Matricardi et al. has been discussed *supra.*

One of ordinary skill in the art would have been motivated to use the irradiation sterilized bacteria of Tarpley et al. in the endotoxin exposure method of inhibiting allergic disease of Gereda et al. because Matricardi et al. teaches that administration of living organisms as probiotics must be regarded as potentially dangerous for infants who have lower colonization resistance and are immunologically naive as compared to adults (In particular, page 465 'Safety' paragraph). Tarpley et al. teaches that bacteria can be irradiation-sterilized. Therefore, it would be advantageous to use endotoxin from irradiated bacteria when administering to infants and children to reduce the risk of infection while preventing allergies.

From the reference teachings, it is apparent that one of ordinary skill in the art would have

had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference, especially in the absence of evidence to the contrary.

13. Claims 1-5, 10, 13, 17-19 and 22-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gereda et al. in view of Matricardi et al. and Previte et al. (PTO-892, Page 2, Reference X).

Gereda et al. has been discussed *supra*.

The claimed invention differs from the prior art by the recitation of irradiation-detoxified lipopolysaccharide or irradiation-detoxified LPS derived from E.coli; wherein the irradiation - detoxified lipopolysaccharide is detoxified by exposure of the endotoxin to irradiation at a level of from about 25 to about 150 KGy; and wherein the irradiation changes the structure of the endotoxin while maintaining its positive immune effect in the resulting irradiation-detoxified lipopolysaccharide.

Previte et al. has been discussed *supra*.

Matricardi et al. has been discussed *supra*.

One of ordinary skill in the art would have been motivated to use the irradiation sterilized bacteria of Previte et al. in the endotoxin exposure method of inhibiting allergic disease of Gereda et al. because Matricardi et al. teaches that administration of living organisms as probiotics must be regarded as potentially dangerous for infants who have lower colonization resistance and are immunologically naive as compared to adults (In particular, page 465 'Safety' paragraph). Previte et al. teaches that lethal moieties of lipopolysaccharide from bacteria can be eliminated using ionizing radiation, while still retaining antigenicity and pyrogenicity. Therefore, it would be advantageous to use irradiated lipopolysaccharide when administering endotoxin to infants and children to reduce the risk of lethality associated with the intact lipopolysaccharide.

From the reference teachings, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference, especially in the absence of evidence to the contrary.

14. Claims 1-5, 10, 13, 17-19 and 22-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Oehling et al. (PTO-892, Page 3, Reference W) in view of Matricardi et al. (IDS filed on 10/04/2004, Reference AN) and Previte et al. (PTO-892, Page 2, Reference W).

Oehling et al. teaches a process for inhibiting development of allergic disease, the process

comprising exposing a neonatal or immature mammal (human) to lipopolysaccharide derived from bacterial endotoxin; (In particular, abstract, Table I); wherein the lipopolysaccharide is adapted to stimulate the Th 1 arm of the immune system; wherein an infant mammal (human) is exposed (In particular, whole document, 'Materials and Methods' section pages 178-180); wherein a human of 1 month to 2 years of age is exposed (In particular, page 178, left column, second to last paragraph); wherein exposure to the lipopolysaccharide is achieved shortly after birth and during the maturing life cycle of the mammal (human) (In particular, page 178, left column, second to last paragraph); wherein exposure is achieved on a daily basis during growth of the mammal (In particular, page 178, right column, second paragraph); wherein exposure is achieved on a weekly basis during growth of the mammal (human) (In particular, page 178, right column, second paragraph).

The claimed invention differs from the prior art by the recitation of irradiation-detoxified lipopolysaccharide or irradiation-detoxified LPS derived from E.coli; wherein the exposure is achieved by administering an aerosol spray composition comprising the lipopolysaccharide; wherein the irradiation -detoxified lipopolysaccharide is detoxified by exposure of the endotoxin to irradiation at a level of from about 25 to about 150 KGy; and wherein the irradiation changes the structure of the endotoxin while maintaining its positive immune effect in the resulting irradiation-detoxified lipopolysaccharide and a process for inhibiting development of allergic disease.

Matricardi et al. has been discussed *supra*.

Previte et al. has been discussed *supra*.

One of ordinary skill in the art would have been motivated to use the irradiation detoxified bacteria of Previte et al. in the bacterial immunotherapy method of inhibiting allergic disease of Oehling et al. because Matricardi et al. teaches that administration of living organisms as probiotics must be regarded as potentially dangerous for infants who have lower colonization resistance and are immunologically naive as compared to adults (In particular, page 465 'Safety' paragraph). Therefore, the bacterial immunotherapy method of Oehling et al. should be safe for use in infants and children and have no risk of toxicity. Previte et al. teaches that isolated LPS and LPS in bacteria can be irradiation-detoxified of its lethal determinants while still retaining antigenicity and pyrogenicity.

All the claims are included in this rejection because the bacterial vaccines containing gram-negative bacteria of Oehling et al. inherently comprise LPS. Claim 4 is included in this rejection because the same product is being given to the same patient. Therefore, the Th1 arm of the immune system is inherently stimulated.

From the reference teachings, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the

invention was made, as evidenced by the reference, especially in the absence of evidence to the contrary.

15. Claims 1-5, 10, 13, 17 and 22-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Oehling et al. (PTO-892, Page 3, Reference V) in view of Matricardi et al. (IDS filed on 01/04/2004, Reference AN) and Tarpley et al. (PTO-892, Page 2, Reference X) as evidenced by Shultz et al. (PTO-892, Page 3, Reference U).

Oehling et al. has been discussed *supra*.

The claimed invention differs from the prior art by the recitation of irradiation-detoxified lipopolysaccharide or irradiation-detoxified LPS derived from E.coli; wherein the exposure is achieved by administering an aerosol spray composition comprising the lipopolysaccharide; wherein the irradiation -detoxified lipopolysaccharide is detoxified by exposure of the endotoxin to irradiation at a level of from about 25 to about 150 KGy; and wherein the irradiation changes the structure of the endotoxin while maintaining its positive immune effect in the resulting irradiation-detoxified lipopolysaccharide.

Matricardi et al. has been discussed *supra*.

Tarpley et al. and Shultz et al. have been discussed *supra*.

One of ordinary skill in the art would have been motivated to use the irradiation sterilized bacteria of Tarpley et al. in the bacterial immunotherapy method of inhibiting allergic disease of Oehling et al. because Matricardi et al. teaches that administration of living organisms as probiotics must be regarded as potentially dangerous for infants who have lower colonization resistance and are immunologically naive as compared to adults (In particular, page 465 'Safety' paragraph). . Tarpley et al. teaches that bacteria can be irradiation-sterilized. Oehling et al. teaches that antibiotics can be administered to clear infections caused by bacterial immunotherapy. It would be advantageous to use a bacterial vaccine with retained immunogenic properties without causing infection and disease, especially when administered to infants and children.

All the claims are included in this rejection because the bacterial vaccines containing gram-negative bacteria of Oehling et al. inherently comprise LPS. Claim 4 is included in this rejection because the same product is being given to the same patient. Therefore, the Th1 arm of the immune system is inherently stimulated.

From the reference teachings, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference, especially in the absence of evidence to the contrary.

16. Claims 1-5, 10, 13, 17, 19 and 22-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tulic et al. in view of Matricardi et al. and Previte et al. (PTO-892, Page 2, Reference X).

Tulic et al., teaches a process for inhibiting development of allergic disease, the process comprising exposing a mammal (human) to lipopolysaccharide derived from bacterial endotoxin (In particular, whole document); wherein the lipopolysaccharide is adapted to stimulate the Th 1 arm of the immune system (In particular, paragraph spanning pages 609-610); wherein the exposure is achieved by administering an aerosol spray composition comprising the lipopolysaccharide (In particular, page 605,'Exposure to LPS' section). Tulic et al. also teaches that microbial infections early in infancy may protect from the later development of atopy and asthma such that the stimulus for normal postnatal maturation of the immunoinflammatory response may be provided by microbial stimulation.

The claimed invention differs from the prior art teachings by the recitation of irradiation-detoxified LPS, wherein an infant mammal is exposed; wherein a human of 1 month to 2 years of age is exposed; wherein exposure to the lipopolysaccharide is achieved shortly after birth and during the maturing life cycle of the mammal; wherein exposure is achieved on a daily basis during the growth of the mammal; wherein exposure is achieved on a weekly basis during the growth of the mammal; a process for inhibiting development of allergic disease a process comprising exposing a mammal to lipopolysaccharide derived from E. coli bacteria endotoxin; wherein a human of 1 month to 2 years of age is exposed.

Matricardi et al. has been discussed *supra*.

Previte et al. has been discussed *supra*.

Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to prevent allergy using bacterial LPS as taught by Tulic et al. with irradiated LPS molecules, especially LPS from E. coli, as taught by Previte et al. because said irradiated LPS molecules are immunostimulatory, less toxic derivatives of LPS, as Matricardi et al. taught is preferred for the treatment of allergy. One of ordinary skill in the art would be especially motivated to treat young humans with the teachings of Matricardi et al, Tulic et al. and Previte et al. because, as Tulic et al. recognizes, microbial infections early in infancy may protect from the later development of atopy and asthma such that the stimulus for normal postnatal maturation of the immunoinflammatory response may be provided by microbial stimulation. One would be motivated to perform the method of Tulic et al. using the various methods taught by Matricardi et al because Matricardi et al. details all the modes of administration that microbial products can be used for prevention of allergies in infants and adults.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

17. No claim is allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nora M. Rooney whose telephone number is (571) 272-9937. The examiner can normally be reached Monday through Friday from 8:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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